MR Spectroscopy in Clinical Practice Course - ISMRM 14th Annual Meeting

Saturday, 6 May 2006

MRI, fMRI and MRS in Epilepsy Surgery

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Introduction

Prognosis of epilepsy disorders in childhood is very diverse, ranging from benign with rapid recovery to the most severe forms with major cognitive and motor deterioration. Many of these malignant forms of epilepsy are related to developmental disorders of the brain, such as cortical malformations, which can be precisely characterized by MRI (1). Many of these epilepsies are refractory to pharmaceutical treatment; therefore neurosurgical treatment might be considered (2). Precise identification of brain structures that exhibit epileptogenic activity is the principal aim of the patient workup performed prior to surgery. Generally, a combination of electroencephalographic (EEG) evaluation and MRI suffices to define seizure localization and the type of epilepsy. If non-invasive methods are not sufficient to draw conclusion about the possibility of surgery, more invasive approaches are employed. This requires implantation of intracranial electrodes, which carries significant risks of morbidity and can be difficult to perform in children.

In this context, quantitative MRI, 1H-MRS, and fMRI are particularly attractive for this group of patients. Furthermore, early metabolic and/or functional deficits, which may occur before structural changes, might provide important findings, earlier in the disease progression.

In this lecture, the rational of using quantitative MRI, fMRI and 1H-MRS or their combination to improve epileptic foci will be given. The implementation of the techniques in clinical environment will be described, and potential artefacts and pitfalls will be discussed.

MRI-based volumetric studies in epilepsy

Temporal lobe epilepsy

Mesio-temporal lobe epilepsy (MTLE) is characterized by hippocampus seizure, which is often associated with hippocampal sclerosis. At term, hippocampal sclerosis leads to cell loss and hippocampal atrophy. Therefore, quantitative volumetric measurement of ipsi- and contralateral hippocampus provides an important clinical criterion of seizure lateralization (3). Manual volumetric assessment of the hippocampus is still the easiest and the most reliable method. In children, hippocampus volumetry gives very similar findings than in adults, with a significant asymmetry against the ipsilateral side (4). Bilateral atrophy has also been reported, with contralateral involvement being correlated with epilepsy duration and impaired psychlogical functioning (5), pointing out the importance to detect and treat epilepsy as early as possible during the childhood.

Extra- Temporal lobe epilepsy

Extra-temporal lobe epilepsy (ETLE) are often more complex to diagnose because of a less well-defined epileptogenic zone. Surgical results in this patient group have been reported to be less favorable than in MTLE patients, and it is felt that this might be due to a more widespread epileptic network. The chance of becoming seizure-free after surgery remains around 70%, whereas is it more

than 85% in MTLE, as illustrated in figure 1 (2, and own data). The goal of modern neuroimaging in ETLE is to improve the detection and localization of epileptic focus. High resolution MRI permits the detection of small dysplasia and migrational defects. Novel MR image analysis methods, such as deformation field mapping, voxel-based morphometry and texture analysis, allows to further detect subtle cortical abnormalities (6). Information provided by quantitative MR imaging of the neocortex may be important for precise diagnosis of surgical candidates, particularly those with "nonlesional" neocortical epilepsy.

Implementation

A single input image is often sufficient for volumetric studies. In general, it is a high-resolution (1 mm^3 spatial resolution) T1-weighted 3D gradient echo sequence obtained in 5-8 minutes (TR/TE/flip 15ms/4.7ms/25°). Inversion-recovery sequences provide excellent contrast for similar scanning time. They become the sequence of choice, especially at 3 Tesla. Either 2D T1-weighted with inversion-recovery (SPIR) or a 3D inversion-recovery turbo gradient echo (MP-RAGE) can be used.

Functional MRI in presurgical evaluation of epilepsy

There are two distinct applications of fMRI in presurgical evaluation of epilepsy; one uses fMRI to localize eloquent cortex before surgery and the other aims to determine the epileptic focus from EEG-correlated fMRI acquisition. The most promising clinical application of presurgical fMRI resides in its ability to determine the dominant hemisphere non-invasively. Ultimately, fMRI may replace the Wada test, which is invasive, difficult to conduct and stressful for the patient. The technique has been validated by different groups using different language component tasks (7, 8). Nevertheless, language fMRI is still limited in children due to the difficulty of performing cognitive tasks in MRI scanners for this group of subjects. Recent investigation shows that hemispheric dominance can be determined in young infants (9), which opens the way of more extended language fMRI evaluation in clinical setting.

EEG-synchronized fMRI in extra-temporal lobe epilepsy

Since initial case reports demonstrating BOLD contrast MRI during seizure (10, 11), a lot of progress has been made in data collection, control of motion as well as data processing. Using scalp EEG to trigger fMRI acquisition (12), it is possible to localize epileptic focus non-invasively in ETLE patients (13, 14). In most patients, it is possible to record good quality EEG inside the magnet (figure 2) allowing triggering fMRI acquisition by interictal discharges. Safety and feasibility studies have been conducted, addressing the important issue of risk of skin burns due to electrodes heating as well as image impairment due to the presence of conductor and electronic device inside the MRI bore (15, 16). These studies showed that the most significant effect is due to RF interaction and care must be observed when using high SAR sequences. As for ECG recording, caution must also be made during wires placement. Conductor positioning close to the transmitter coil and conductor loops must be absolutely avoided, in order to prevent electromotive force V generated either by direct capacitive coupling ($V \propto E \cdot d$; E = E-field, d = wire length) or by inductive coupling ($V \propto \omega \cdot B_1 \cdot A$, = RF frequency, B_1 = amplitude of the RF magnetic field, A = loop area).

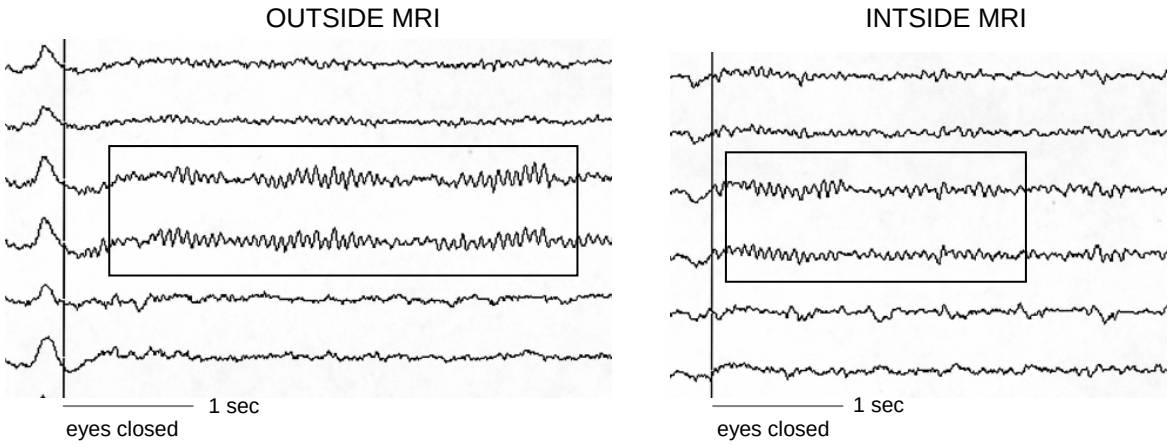

Figure 2: EEG recording outside (left) and inside (right) a 1.5 T magnet. Alpha rhythm initiated just after eyes closing (box) is clearly identified at the 2 occipital electrodes. Topography and freuency patterns are identical inside and outside the magnet.

Hundreds of patients were examined by different epilepsy center using EEG-triggered fMRI. EEG-fMRI examinations often revealed discrete area of activation, concordant with other clinical findings or by invasive recording. Nevertheless, in some cases (10-20% according to different research groups), EEG-fMRI is not concordant with the standard presurgical evaluation (17, 18). These negative findings may be due to more complex epilepsy pattern, false activation due to spatial smoothing of downstream venous contribution to the BOLD signal (19). In this case, 1H-MR spectroscopy can be used to distinguish pathological region with “true” activation from regions with vascular-related signal change (type 2 BOLD effect). Another possibility may be due to rapid propagation of epileptical activity. In this case, fMRI alone would not be able to resolve the time frame of such activity. However, rapid propagation can be derived from EEG source localization (20), and the combination of these two complementary methods might be able to resolve the spatio-temporal pattern of these complex extra-temporal epilepsies (21).

With the advent of 128-channel (and more) EEG recording, more precise correspondence between 3D EEG source localization and fMRI can be obtained. Figure 3 illustrates a case with right neocortical temporal lobe epilepsy. EEG-fMRI and 3D EEG source localization were concordant in the sense that both techniques revealed a predominant epileptic activity in the right temporal lobe. But some difference also exists; for instance, EEG-fMRI showed activations more anterior than the 3D-EEG source. Interestingly, intracranial EEG recording (fig. 3c) found an onset located in the anterior pole of the temporal cortex, with propagation toward more posterior regions of the temporal lobe.

The major limitations of EEG-fMRI are 1) the difficulty to efficiently remove MRI-induced artifacts on the EEG and 2) the signal void due to susceptibility artifacts close to air cavities. Progress has been mode lately to improve the MRI-compatible EEG systems. Up to 64 (even 128) channels EEG systems are proposed on the market, which allow in principle the suppression of MRI-induces artifacts (22). Susceptibility artifacts can be reduced as well, with the use of parallel imaging techniques such SENSE. Thus, despite these still limiting issues, information provided by EEG-fMRI together with other modalities will be of great benefit to epilepsy patients. At term, non-lesional extratemporal lobe epileptic patients, especially children, will fully benefit from neurosurgery.

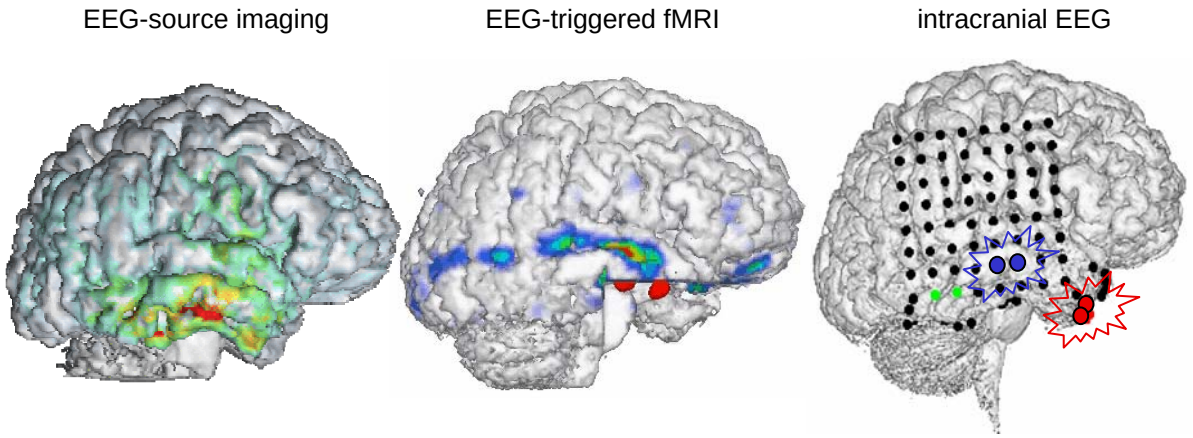

Figure 3: Pharmaco resistant epilepsy of the right temporal lobe. 3D EEG source (a) using 128-electrode is consistent with EEG-fMRI (b). FMRI revealed also more anterior activation, which is consistent with intracranial EEG recording (c). This phase 2 investigation demonstrates that seizure onset was located in the anterior pole (red electrodes), with a very rapid propagation (tens of msec) to the posterior part of the temporal lobe.

Implementation

Similar to BOLD fMRI, the method of choice is gradient echo EPI. In general, whole brain coverage is used together with SENSE (acceleration factor 2). The major difference is the long and irregular delay between consecutive image acquisitions due to the uncontrolled occurrence of spikes. Typically, TR must be large enough (TR>16sec) and the flip angle somewhat reduced (80˚) to avoid T1 saturation effects between scans. In practice, event-related triggered fMRI is also feasible (23). This approach has the advantage to acquire multiple volumes after the detection of a spike, instead of a single one. Thus, more data per event (spike) can be used in the statistical analysis, increasing its sensitivity to detect true activation. Another consequence of ER-triggered fMRI is the possibility to reduce the number of spike necessary for the acquisition. As a result, the total examination time can be considerably shortened, reducing then the risk of motion artifact that may be important in children. Other acquisition scheme using continuous acquisition was proposed (15). As for ER-triggered fMRI, this scheme requires to be able to record continuously the EEG during MRI acquisition (24).

In practice, a good alternative is to acquire a spike-related burst of volumes (figure 4). Typically five image volumes can be acquired before the BOLD response vanishes. In this case, no EEG during MRI acquisition is mandatory. This time series is then compared with fMRI acquisition not related to a spike event (control condition). Each time point is tested individually (25), and the time-point *z-score* maps are averaged in order to keep the most relevant activation foci (26).

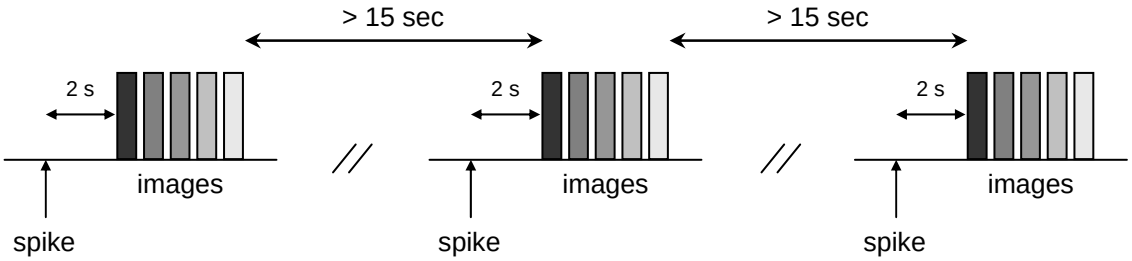

Figure 4: Diagram of the “burst” image acquisition protocol. A limited series of volume images is acquired after each event spike.

1H-MRS in presurgical evaluation of epilepsy

MR spectroscopy using 31P or 1H moieties have been used in the context of epilepsy research. Nevertheless, only 1H-MRS is used clinically in presurgical epilepsy evaluation. 1H-MRS reveals the diseased focus by showing a reduction in NAA and NAA-ratio (27), with a rise in lactate during acute seizure, which reflects neuronal loss and bioenergetics compromise in the excitable cells in the epileptogenic area first described by Matthews et al in 2 patients with Rasmussen's syndrome (28). The main hypothesis behind the use of 1H-MRS in epilepsy surgery is that repeated seizure activity is associated with neuronal loss. Decreased NAA indicates the degree of this neuronal loss and provides a sensitive marker for epileptic focus localization.

Mesio-Temporal lobe epilepsy (MTLE)

Correct lateralization of the seizure onset with 1H-MRS was found on average in 80 to 90% of the patients with unilateral temporal focus showed decreased NAA/Cr or NAA/(Cho+Cr) values ipsilateral to the focus. This was also true for patients with non-lesional temporal epilepsy (29), indicating that MRS is a sensitive tool and may depict even discrete histopathological changes.

Interestingly, up to 50% of the patients revealed also contralateral abnormalities, both in adult and pediatric series. Given the fact that bilateral low intensity values do not preclude good surgical outcome, it is suggested that decreased NAA values or NAA-depending ratios reflect only functional, i.e. transient changes (30, 31). However, presurgical spectra of the resected temporal lobe are also abnormally low and associated to «real» pathological tissue as determined by post-operative histological analysis. In an autopsy study of patients with TLE, abnormalities in both hippocampi were found in 30% of the cases (32), indicating that contralateral hippocampal and neocortical low NAA/(Cho+Cr) reflect indeed tissue abnormalities although they might not be necessarily as epileptogenic as the ipsilateral side. If the presence (and degree) or absence of contralateral NAA changes depends on specific clinical variables has not yet been thoroughly investigated.

Extra-temporal lobe epilepsy (ETLE)

There are only few MRS studies in patients with extratemporal epilepsy (ETLE) measuring metabolites in extratemporal tissue (33, 34). The localizing or lateralizing value seems to be less favorable than in MTLE patients, probably to a less well-defined epileptogenic zone and/or «incorrectly» placed voxel. Most of the examined ETLE patients had frontal lobe epilepsy. Surgical results in this patient group have been reported less favorable than in MTLE patients, and it is felt that this is due to a more widespread network. Measuring the metabolite ratios in the mesio-temporal structures in ETLE patients yielded diminished values ipsilateral to the focus (35) indicating widespread changes outside the focus proper (36). Thus, while MTLE patients were extensively studied, the use of MRS in patients with ETLE is less well defined and, it seems, less well exploited.

Therefore, the goal of modern neuroimaging is to improve the detection and localization of extratemporal epileptic activity. Transmantle dysplasia shows decreased NAA and NAA/Cr levels, which may serve as a sensitive indicator to confirm cortical malformation. During status epilepticus, the FLAIR technique may provide a good contrast associated with the edema due to prolonged seizure activity. When such localization exists, 1H-MRS shows reduced NAA level and an increase of lactate (figure 5). Whereas lactate returns to normal several days after the status, NAA level remains abnormally low and may serve as an indicator for extratemporal epileptic focus, even in absence of MRI visible lesion (37).

Figure 5: 1H-MRS (TE = 288 ms) of a extratemporal lobe epilepsy in a 8-years-old child. The data have been taken few hours after status epilepticus, wich is expressed by an edema seen on the FLAIR image. This edema was transient, and disapeared after few days. The 1H-MRS spectrum (left) shows a low NAA level, suggesting abnormal cortex or neuronal loss. The split lactate peak (1.3 ppm) reflects prolonged epileptic neuronal activity in the active focus.

Another alternative in absence of lesion on conventional MRI is the use of EEG-fMRI to guide MRS voxel placement (38). All these techniques provide non-invasive means of investigating brain metabolism in children, and are already well integrated to routine MRI examination. There is little doubt that they will contribute to better identify and characterize seizure focus.

Implementation

Most of clinical scanner offers STEAM or PRESS sequences for localized 1H-MRS. Because most of the time, reduces NAA and increased lactate level are sufficient to obtain a diagnosis, long echo time (TE = 288 ms) is often chosen. Both hippocampi MRS take around 15 minutes of acquisition. Metabolite normalization (not accounted for relaxation effects) cans easily be performed off-line using LCModel.

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